

PB88-219373

Health and Environmental
Effects Profile for Benzotrichloride

(U.S.) Environmental Protection Agency
Cincinnati, OH

Jul 86



U.S. Department of Commerce
National Technical Information Service

NTIS

TECHNICAL REPORT DATA (Please read instructions on the reverse before completing)		
1. REPORT NO. EPA/600/X-86/194	2.	3. RECIPIENT'S ACCESSION NO. PB88-219373
4. TITLE AND SUBTITLE Health and Environmental Effects Profile for Benzotrichloride		5. REPORT DATE July 1986
		6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)		8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS		10. PROGRAM ELEMENT NO.
		11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268		13. TYPE OF REPORT AND PERIOD COVERED
		14. SPONSORING AGENCY CODE EPA/600/22
15. SUPPLEMENTARY NOTES		
16. ABSTRACT The Health and Environmental Effects Profile for <u>Benzotrichloride</u> was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. <u>Benzotrichloride</u> has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for <u>benzotrichloride</u> is $12.63 \text{ (mg/kg/day)}^{-1}$ for oral exposure. The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for <u>benzotrichloride</u> is 10.		
17. KEY WORDS AND DOCUMENT ANALYSIS		
a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field Group
18. DISTRIBUTION STATEMENT Public	19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES 73
	20. SECURITY CLASS (This page) Unclassified	22. PRICE A04 14.95

EPA/600/X-86/194
July 1986

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE
FOR BENZOTRICHLORIDE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
National Technical Information Service
SPRINGFIELD, VA. 22161

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEP's are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEP's will become part of the EPA RCRA and CERCLA dockets.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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EXECUTIVE SUMMARY

Benzotrichloride is a colorless to yellowish liquid with a penetrating odor. It is made by chlorinating boiling toluene in the presence of light and phosphorus trichloride (Windholz, 1983; Hawley, 1981). The major use of benzotrichloride is in the manufacture of benzoyl chloride (Gelfand, 1979), and in the dye industry for the production of malachite green, rosamine, quinoline red and alizarin yellow A (Sidi, 1964). Lesser amounts are used to make benzotrifluoride, as a dyestuff intermediate, and in producing hydroxybenzophenone UV light stabilizers (Gelfand, 1979).

The primary fate mechanism for benzotrichloride in the environment is hydrolysis. From the rate constant values (Mabey and Mill, 1978; Laughton and Robertson, 1959) the hydrolysis half-lives have been estimated to be 11 seconds at 25°C (pH 7) and 3 minutes at 5.10°C. Because benzotrichloride hydrolyzes rapidly, it is not expected to persist in the environment. It may, however, persist longer in dry air and soil, and in air, water and soil in cold climates.

Since benzotrichloride has no known consumer uses, exposure to this chemical is likely to occur from occupational settings. Exposure of the general population to industrial fugitive emissions is not expected to be significant since benzotrichloride hydrolyzes rapidly in the presence of moisture (Windholz, 1983).

There is little information available concerning the toxicity of benzotrichloride to aquatic organisms. It is relatively nontoxic to fish, having a 48-hour LC_{50} of ~4 g/l in the only species tested, Leuciscus idus, (Juhnke and Luedemann, 1978). However, this value may be questionable since it is greater than the reported solubility in water and since benzotrichloride hydrolyzes rapidly in water. In other bioassays, LC_{50} values

could not be determined because the concentrations tested were not high enough to cause significant mortality. Sublethal effects were observed in other species, with the most sensitive effect being the toxic threshold for inhibition of cell multiplication in the protozoan, Chilomonas paramecium, at 27 mg/l (Bringmann and Kuehn, 1981, 1982).

Pharmacokinetic studies of benzotrichloride are limited. Benzotrichloride or its hydrolysis product, benzoic acid, was rapidly and extensively absorbed from the gastrointestinal tract of rats; peak blood levels of radioactivity were reached within 4 hours and >90% of the dose of radioactivity was excreted in the urine collected for 48 hours after oral dosing with ^{14}C -benzotrichloride (Yu and Nietschmann, 1980). A half-life for absorption was estimated to be 3 hours, while the half-life for elimination from blood was 22 hours. Radioactivity was distributed rapidly to the tissues, with the highest levels occurring in fat, followed by the kidneys and liver. Radioactivity disappeared from all tissues with an average half-life of 14 hours. Benzotrichloride was hydrolyzed to benzoic acid, which was conjugated with glycine to form hippuric acid, the major urinary metabolite. Urinary and fecal excretion of radioactivity was >90% and ~10%, respectively, at 48 hours. The half-life for urinary excretion was 8 hours.

Evidence that benzotrichloride is carcinogenic was available for animal and human studies. Oral administration of benzotrichloride to female mice at 0, 0.043, 0.17, 0.7 or 2.7 mg/mouse, 2 days/week (0, 0.4, 1.6, 6.7, 25.7 mg/kg/day, using 0.03 kg as the mouse weight) for 25 weeks followed by ~1 year of observation resulted in dose-related, significantly increased incidences of squamous cell carcinoma of the forestomach at ≥ 6.7 mg/kg/day and of lung adenoma/adenocarcinoma at ≥ 1.6 mg/kg/day and a significantly increased incidence of thymoma at 25.7 mg/kg/day (Fukuda et al., 1978).

Inhalation exposure of female mice to 1.6 ppm (12.8 mg/m³) for 30 minutes, 2 days/week for 12 months followed by an observation period of 12-15 months, resulted in a high incidence of lung tumors (Yoshimura et al., 1979). Similar results were obtained in female mice exposed by inhalation to 6.8 ppm (54 mg/m³) for 30 minutes, twice weekly for 5 months followed by 5 months of observation (Takemoto et al., 1978). No controls were used in these studies. Fukuda et al. (1981) found increased incidences of skin carcinoma, lung adenoma/carcinoma and lymphoma of the thymus in female mice treated dermally with benzotrichloride in benzene compared with benzene-treated controls. In humans, data regarding the carcinogenic effect of benzotrichloride exposure alone were not available. Increased incidences of digestive and respiratory cancers were found among workers exposed to benzotrichloride, benzal chloride, benzyl chloride and toluene in the manufacture of benzoyl chloride and other chlorinated toluenes (Sakabe et al., 1976; Sakabe and Fukuda, 1977; Sorahan et al., 1983).

Results of mutagenicity tests of benzotrichloride in bacterial systems are equivocal. Yasuo et al. (1978) obtained positive results in a rec assay in Bacillus subtilis and in reverse mutation assays in Escherichia coli and Salmonella typhimurium in the presence of metabolic activation. Jagannath (1978), however, found negative results for reverse mutation in S. typhimurium and for forward mutation in Saccharomyces cerevisiae in the presence and absence of metabolic activation.

The teratogenicity of benzotrichloride has been studied in rats. Gavage administration of benzotrichloride to pregnant rats on days 6-15 of gestation at dose levels of 0, 12.5, 25 or 50 mg/kg/day resulted in reduced mean fetal weight at all doses, skeletal anomalies at unspecified doses and increased numbers of resorptions and reduced litter sizes at 50 mg/kg/day (Ruddick et al., 1982).

In long-term studies, increased mortality was observed in female mice treated by gavage with 0.7 or 2.7 mg/mouse, 2 days/week for 25 weeks (Fukuda et al., 1978). In addition to increased incidences of stomach tumors, other proliferative stomach lesions were observed at unspecified doses. Dietary treatment of rats for 28 days resulted in increased serum levels of sorbitol dehydrogenase and dose-related increased incidence and severity of lesions in the liver, kidneys and thyroid at ≥ 0.5 ppm (Chu et al., 1984). The oral LD_{50} of benzotrichloride is 807 mg/kg for mice (Dean, 1978) and 736 mg/kg for rats (Dean, 1979).

High mortality was observed in female mice exposed by inhalation to 1.6 ppm (12.8 mg/m³), 2 days/week for 12 months (Yoshimura et al., 1979) or to 6.8 ppm (54 mg/m³), 2 days/week for 5 months (Takemoto et al., 1978). In addition to the high incidences of lung tumors in these mice, other proliferative lesions were observed in the respiratory tract. There were also inflammation and hypertrophy of lymph nodes, liver, spleen and kidneys. Lung congestion, inflammatory cell infiltration, degeneration, desquamation, ulceration and squamous metaplasia were observed in the respiratory tract of rats exposed by inhalation to 48.2 or 460 mg/m³, 6 hours/day, 5 days/week for 4 weeks (Levin, 1981). Rats exposed to 48.2 mg/m³ had reduced body weight and dyspnea, while all rats exposed to 460 mg/m³ had severe dyspnea and died during the first week. The 1-hour inhalation LC_{50} of benzotrichloride is 8390 mg/m³ for rats (Cavender, 1979).

An RQ of 10 for chronic toxicity was derived based on increased mortality of female mice exposed by inhalation to benzotrichloride in the study by Yoshimura et al. (1979). A q_1^* of $12.63 \text{ (mg/kg/day)}^{-1}$ and an F factor of $88 \text{ (mg/kg/day)}^{-1}$ were derived based on the dose-response data for adenocarcinomas in the lungs of female mice treated orally by Fukuda et al.

(1978). The concentrations in water associated with increased lifetime risks of 10^{-5} , 10^{-6} and 10^{-7} are 2.8×10^{-5} , 2.8×10^{-6} and 2.8×10^{-7} mg/l, respectively. Benzotrachloride is a Potency Group 2 chemical with an IARC classification of 2B, a CAG classification of group B₂, and MEDIUM ranking in the Hazard Ranking Scheme under CERCLA.

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LIST OF ABBREVIATIONS

CAS	Chemical Abstract Service
CS	Composite score
EC ₅₀	Concentration effective to 50% of recipients
GC/MS	Gas chromatography/mass spectrometry
IR	Infrared
K _{ow}	Octanol/water partition coefficient
LC ₅₀	Concentration lethal to 50% of recipients
LD ₅₀	Dose lethal to 50% of recipients
MED	Minimum effective dose
ppm	Parts per million
RQ	Reportable quantity
RV _d	Dose-rating value
RV _e	Effect-rating value
SMR	Standard mortality ratio
TLC	Thin-layer chromatography
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Synonyms for benzotrichloride include: benzene, trichloromethyl; toluene, α,α,α -trichloro-; α,α,α -trichlorotoluene; α,α',α'' -trichlorotoluene; (trichloromethyl) benzene; phenylchloroform; ω,ω,ω -trichlorotoluene; benzenyl trichloride; and toluene trichloride. The structure, molecular weight, empirical formula and CAS Registry number of benzotrichloride are listed below.



Molecular weight: 195.48

Empirical formula: $\text{C}_7\text{H}_5\text{Cl}_3$

CAS Registry number: 98-07-7

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Benzotrichloride is a colorless to yellowish liquid with a penetrating odor (Hawley, 1981). Selected physical properties are listed below:

Melting point:	-5.0°C	Windholz, 1983
Boiling point: (at 1 atm)	220.8°C	Windholz, 1983
Density: (g/cm ³) at 20°C/4°C	1.3756	Windholz, 1983
Vapor pressure, mm Hg:	0.23 at 20°C	Weber et al., 1981
Water solubility, mg/l:	53 at 5°C 250 at 30°C	Ohnishi and Tanabe, 1971
Nonaqueous solubility:	soluble in alcohol, benzene and ether	Windholz, 1983

Log K _{ow} :	2.92	Hansch and Leo, 1981
Refractive index, 20°C:	1.55789	Gelfand, 1979
Vapor density (air = 1):	6.77	Gelfand, 1979
Flash point:		
Fisher tag closed cup	>99°C	Gelfand, 1979
Cleveland open cup	127°C	Gelfand, 1979

1.3. PRODUCTION DATA

Velsicol Chemical Corporation in Chattanooga, TN, appears to be the only company manufacturing benzotrichloride as of January, 1985 (SRI, 1985). The TSCA inventory listed Velsicol Chemical Corporation, Chattanooga, TN; Hooker Chemical and Plastics, Niagara Falls, NY; and a third company, which was considered confidential, as producers of benzotrichloride (U.S. EPA, 1977). The only production volume data available was that Hooker Chemical and Plastics produced 10-50 million pounds of benzotrichloride in 1977 (U.S. EPA, 1977).

Benzotrichloride is made by chlorinating boiling toluene in the presence of light and 2% phosphorus trichloride (Windholz, 1983). The crude product is purged with inert gas to remove hydrogen chloride and then used directly or purified by distillation (Gelfand, 1979).

1.4. USE DATA

Benzotrichloride is used extensively in the dye industry for the production of malachite green, rosamine, quinoline red and alizarin yellow A (Sidi, 1964). Benzotrichloride is also used in the manufacture of benzoyl chloride (Gelfand, 1979). Lesser amounts are used to make benzotrifluoride, as a dyestuff intermediate, and in producing hydroxybenzophenone UV light stabilizers (Gelfand, 1979).

1.5. SUMMARY

Benzotrichloride is a colorless to yellowish liquid with a penetrating odor. It is made by chlorinating boiling toluene in the presence of light and phosphorus trichloride (Windholz, 1983; Hawley, 1981). The major use of benzotrichloride is in the manufacture of benzoyl chloride (Gelfand, 1979). Lesser amounts are used to make benzotrifluoride, as a dyestuff intermediate, and in producing hydroxybenzophenone UV light stabilizers (Gelfand, 1979).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

In the presence of water, benzotrichloride will hydrolyze rapidly, forming benzoic and hydrochloric acids (Windholz, 1983). Mabey and Mill (1978) reported the hydrolysis rate constant for benzotrichloride at 25°C and pH of 7 to be $6.3 \times 10^{-2} \text{ sec}^{-1}$. Therefore, its estimated half-life in neutral water at 25°C is 11 seconds. Laughton and Robertson (1959) found that the hydrolysis rate constant for benzotrichloride at 5.10°C was $387 \times 10^{-5} \text{ sec}^{-1}$, which corresponds to a half-life of 3.0 minutes. Thus, benzotrichloride will rapidly decompose in soil, moist air and water, and will not persist when released to aquatic environments. Because of its rapid hydrolysis, partitioning in and transport from aquatic systems will not be significant.

2.2. AIR

Benzotrichloride released to the air will hydrolyze rapidly in the presence of moisture in the atmosphere. If benzotrichloride were to remain in the vapor phase, the estimated atmospheric half-life is ~2 days at an OH radical concentration of $8 \times 10^5 \text{ molecules/cm}^3$ which is due to its reaction with OH radicals (U.S. EPA, 1985).

2.3. SOIL

As in the water and air, benzotrichloride will hydrolyze rapidly in moist soil. Degradation will be slower in arid soils.

2.4. SUMMARY

The primary fate mechanism for benzotrichloride in the environment is hydrolysis. From the rate constant values (Mabey and Mill, 1978; Laughton and Robertson, 1959), the hydrolysis half-lives have been estimated to be 11 seconds at 25°C (pH 7) and 3 minutes at 5.10°C. Because benzotrichloride

hydrolyzes rapidly, it is not expected to persist in the environment. It may, however, persist longer in dry air and soil, and in air, water and soil in cold climates.

3. EXPOSURE

3.1. WATER

Shafer et al. (1984) reported that benzotrichloride may have been present in a hazardous waste soil sample, but even though GC/MS and GC/IR were used, its presence could not be confirmed. Because benzotrichloride hydrolyzes rapidly, even if the compound were present in soil, it is unlikely that benzotrichloride would leach into groundwater.

3.2. FOOD

Pertinent data regarding the presence of benzotrichloride in food could not be located in the available literature as cited in the Appendix. Since benzotrichloride hydrolyzes rapidly, it is not expected to be present in foods that contain water.

3.3. INHALATION

Pertinent data regarding the exposure to benzotrichloride in the air could not be located in the available literature as cited in the Appendix. The most likely source for exposure is in areas where it is produced and used. Little exposure is expected outside of these areas since benzotrichloride will probably hydrolyze rapidly before reaching the general population.

3.4. SUMMARY

Since benzotrichloride has no known consumer uses, exposure to this chemical is likely to occur from occupational settings. Exposure to the general population from industrial fugitive emissions is not expected to be significant since benzotrichloride hydrolyzes rapidly in the presence of moisture (Windholz, 1983).

4. PHARMACOKINETICS

4.1. ABSORPTION

Yu and Nietschmann (1980) administered a single dose of ~40 mg/kg of ^{14}C -benzotrichloride (uniformly ring-labeled) in corn oil by gavage to groups of 3 male and 15 female weanling Sprague-Dawley albino rats. A maximum blood level of radioactivity of 6.5 ppm was reached 4 hours after dosing. A half-life for absorption of 3 hours was estimated from the blood vs. time curve. At 8 and 48 hours after dosing, ~50 and >90%, respectively, of the radioactivity were excreted in the urine. These results indicate that benzotrichloride or its hydrolysis product, benzoic acid, was rapidly and extensively absorbed from the gastrointestinal tract of rats.

4.2. DISTRIBUTION

The tissue distribution of radioactivity was evaluated following a single oral dose of ^{14}C -benzotrichloride administered to male and female rats (Yu and Nietschmann, 1980). The half-life for elimination from blood was 22 hours. Benzotrichloride was distributed rapidly to tissues. Radioactivity levels in fat tissues were higher than in other tissues, being 56 ppm after 8 hours and 4 ppm after 72 hours. Elimination of radioactivity from fat, however, occurred at a rate similar to that of other tissues. The average half-life for elimination from the tissues was ~14 hours. The kidneys and liver contained the next highest levels of radioactivity, with 20 ppm after 8 hours and 2 ppm after 72 hours, while the muscle, brain and heart had the lowest residue levels.

4.3. METABOLISM

Urinary metabolites of benzotrichloride were isolated and identified in the urine of female rats administered a single oral dose of uniformly ring-labeled ^{14}C -benzotrichloride (~40 mg/kg) (Yu and Nietschmann, 1980). TLC

analysis revealed that 91% of the radioactivity in the urine was hippuric acid. Benzoic acid and phenylacetic acid each accounted for ~0.8% of the urinary radioactivity. Four unidentified metabolites accounted for 5.5%. No unchanged parent compound was found in the urine. Yu and Nietschmann (1980) suggested that hydrolysis of benzotrichloride to benzoic acid in the tissue was followed by conjugation of benzoic acid with glycine to form hippuric acid, which was excreted in the urine.

4.4. EXCRETION

The disposition of benzotrichloride was determined in male and female rats administered ~40 mg/kg ^{14}C -benzotrichloride in corn oil by gavage (Yu and Nietschmann, 1980). Of the administered radioactivity, ~85% was excreted in the urine in 24 hours and >90% was excreted in the urine in 48 hours. Fecal excretion of radioactivity amounted to ~10% in 48 hours. Excretion was complete at 72 hours. The half-life of urine elimination was 8 hours.

4.5. SUMMARY

Benzotrichloride or its hydrolysis product, benzoic acid, was rapidly and extensively absorbed from the gastrointestinal tract of rats; peak blood levels of radioactivity were reached within 4 hours, and >90% of the dose of radioactivity was excreted in the urine collected for 48 hours after oral dosing with ^{14}C -benzotrichloride (Yu and Nietschmann, 1980). A half-life for absorption of 3 hours was estimated, while the half-life for elimination from blood was 22 hours. Radioactivity was distributed rapidly to the tissues, with the highest levels in fat, followed by the kidneys and liver. Radioactivity disappeared from all tissues with an average half-life of 14 hours. Benzotrichloride was hydrolyzed to benzoic acid, which was conjugated with glycine to form hippuric acid, the major urinary metabolite.

Urinary and fecal excretion of radioactivity was >90% and ~10%, respectively, at 48 hours. The half-life for urinary excretion was 8 hours, thus indicating that benzotrichloride or its hydrolysis product, benzoic acid, was rapidly and extensively absorbed from the gastrointestinal tract of rats.

5. EFFECTS

5.1. CARCINOGENICITY

5.1.1. **Animal Studies.** Several experiments using laboratory animals have established the carcinogenicity of benzotrichloride using different routes of administration. Groups of forty 9-week-old female ICR mice were given gavage doses of 0.0, 0.0315, 0.125, 0.5 or 2 μ l (0.0, 0.043, 0.17, 0.7 or 2.7 mg/mouse) benzotrichloride in 0.1 ml sesame oil twice weekly for 25 weeks (Fukuda et al., 1978). At 18 months after the start of treatment, surviving mice were killed and histological examinations of these mice and some mice that died during the experiment were performed. High rates of mortality were observed in the two highest dose groups. In the group given the highest dose, 50% mortality was reached at 6.5 months, while in the group given the next highest dose, 50% mortality was reached at 16.4 months. The other treated groups did not reach 50% mortality by the end of the 18-month period. Further information regarding mortality was not provided. The incidences of treatment-related tumors are presented in Table 5-1. The incidences of squamous cell carcinoma of the forestomach and pulmonary adenomas in the two highest dose groups, of pulmonary adenocarcinoma in the three highest dose groups and of thymoma in the highest dose group were significantly increased compared with controls.

Yoshimura et al. (1979) exposed a group of 37 five-week-old female ICR-ICL mice to an average concentration of 1.6 ppm (12.8 mg/m³) benzotrichloride vapor for 30 minutes, twice weekly for 12 months at room temperature. The mice were observed for an additional 12 or 15 months after which time they were killed. No controls were maintained. Histopathological examination of the 10 mice that died before 12 months revealed benign lung adenomas in 3/10 mice and lung adenocarcinomas in 1/10 mice. In the 10 mice

TABLE 5-1

Incidences of Tumors in ICR Female Mice Treated by Gavage with
Benzotrichloride in Sesame Oil for 25 Weeks and Killed 18 Months After
the Start of the Experiment^a

Target Organ	Tumor Type	Dose ^b (mg/kg/day)	Tumor Incidence ^c (p value)
Forestomach	squamous cell carcinoma	0.0	0/35 (NS)
		0.4	0/37 (NS)
		1.6	2/38 (NS)
		6.7	22/40 (<0.001)
		25.7	24/35 (<0.001)
	noninvasive carcinoma ^d	0.0	0/35 (NS)
		0.4	1/37 (NS)
		1.6	2/38 (NS)
		6.7	3/40 (NS)
		25.7	2/35 (NS)
Lung	adenocarcinoma	0.0	0/35 (NS)
		0.4	1/37 (NS)
		1.6	9/38 (<0.001)
		6.7	16/40 (<0.001)
		25.7	10/35 (<0.001)
	adenoma	0.0	1/35 (NS)
		0.4	0/37 (NS)
		1.6	6/38 (NS)
		6.7	17/40 (<0.001)
		25.7	10/35 (<0.001)
Thymus	thymoma	0.0	0/35 (NS)
		0.4	0/37 (NS)
		1.6	1/38 (NS)
		6.7	2/40 (NS)
		25.7	7/35 (<0.001)

TABLE 5-1 (cont.)

QUALITY OF EVIDENCE

Strengths of Study: The mice were treated by a relevant route at several doses and observed for a significant portion of the lifespan. Comprehensive histological examination was performed.

Weakness of Study: Only one sex of one species was studied.

Overall Adequacy: Adequate

^aSource: Fukuda et al., 1978

^bThe doses in mg/kg/day were calculated by dividing the amount administered (see text) by 0.03 kg (the reference mouse body weight) and by multiplying by 2 days/7 days.

^cFischer Exact test performed at SRC

^dThe noninvasive carcinomas in the forestomach were regarded as benign.

NS = Not significant

killed at the end of the 12-month exposure period, pulmonary adenocarcinoma was found in 4/10 and adenoma in 5/10. Of eight mice that died between 12 and 15 months, three had pulmonary adenomas and three had pulmonary adenocarcinomas. Nine mice were killed at 15 months; five had adenocarcinomas, two had adenomas. High incidences of epithelial proliferation in the trachea and bronchi were also observed.

Takemoto et al. (1978) exposed a group of 32 five-week-old ICR mice by inhalation to an average concentration of 6.8 ppm (54 mg/m³) benzotrichloride for 30 minutes, twice weekly for 5 months, followed by a 1- or 5-month observation period. No controls were maintained. Of 12 mice that died during the exposure period, 2 had pulmonary adenomas. After 6 months of treatment, 6/11 mice developed lung tumors (benign adenoma) and one mouse had skin squamous cell carcinoma. At the end of the experiment (10 months), 8/9 had pulmonary adenomas and 1/9 had a pulmonary adenocarcinoma, 3/9 had skin squamous cell carcinoma and 4/9 had skin papillomas. The incidence of leukemia was 8/32. Because controls were not used, the significance of the tumor data cannot be assessed.

Fukuda et al. (1981) conducted a series of skin-painting experiments in one strain of mice to investigate the carcinogenicity of benzotrichloride. In the first experiment, three groups of 19-22 female ICR mice (14 weeks old) received skin applications (on the back of each mouse clipped before treatment and repeated as necessary) of 25 μ l benzene (vehicle control), 25 μ l benzotrichloride (purity unspecified) or 25 μ l of a 50% solution of benzotrichloride in benzene twice weekly for 3 weeks and then once weekly until the mice were killed at 7.2 months. Mortality at the end of the experiment was 0, 10 and 40% in the control, low- and high-dose groups, respectively. The incidence of tumors is presented in Table 5-2.

TABLE 5-2
Incidence of Tumors in Female ICR Mice Treated Dermal with Reagent Grade Benzotrichloride*

Experiment Number	Dose (μ g benzotrichloride/painting)	Duration of Treatment (months)	Duration of Study (months)	Vehicle	Target Organ	Tumor Type	Tumor Incidence
I	25	7.2	7.2	none	skin lung thymus	carcinoma adenoma/carcinoma lymphoma	12/22 9/22 6/22
	12.5	7.2	7.2	benzene	skin lung thymus	carcinoma adenoma/carcinoma lymphoma	6/19 10/19 1/19
	0	7.2	7.2	benzene only	skin lung thymus	carcinoma adenoma/carcinoma lymphoma	0/20 0/20 0/20
II	10	5.7	5.7	none	skin lung thymus	carcinoma adenoma/carcinoma lymphoma	4/9 3/9 5/9
	5	9.8	9.8	benzene	skin lung thymus	carcinoma adenoma/carcinoma lymphoma	7/10 10/10 3/10
	0	9.8	9.8	benzene only	skin lung thymus	carcinoma adenoma/carcinoma lymphoma	0/10 0/10 0/10
III	2.3 diluted with benzene to 25 μ g	11.7	13.3	benzene	skin lung	carcinoma adenoma/carcinoma	13/19 11/19
	0	11.7	18.7	benzene only	skin lung	carcinoma adenoma/carcinoma	0/20 2/20

Quality of Evidence

Strengths of Study: Benzotrichloride was administered at several different dose levels and durations, resulting in dose-related incidence data. Appropriate vehicle controls were included.

Weakness of Study: The compound was applied dermally, with no apparent prevention of oral and inhalation exposure. Only female mice were treated.

Overall Adequacy: Limited

*Source: Fukuda et al., 1981

In the second experiment, three groups of ten 3-week-old ICR female mice were skin-painted with 10 μ l of benzene (vehicle control), 10 μ l benzotrichloride or 10 μ l of a 50% solution of benzotrichloride in benzene 3 times/week for 4 weeks, and 2 times/week thereafter until the mice were killed at 9.8 months. The mice treated with 10 μ l of benzotrichloride were killed at 5.7 months because of high mortality and morbidity. Mortality at termination was 0, 60 and 80% for the control, low- and high-dose groups, respectively. The incidences of skin carcinomas, lung adenomas/carcinomas and lymphomas are presented in Table 5-2. In addition, two squamous-cell carcinomas of the lips and one squamous-cell carcinoma of the forestomach were reported in the low-dose mice. These tumors were assumed to result from the oral ingestion of benzotrichloride, which was caused by licking of the skin.

In the third experiment, two groups of 20 seven-week-old female mice of the same strain received skin applications of 25 μ l benzene (controls) or 25 μ l of a 9.2% solution of benzotrichloride in benzene twice weekly for 11.7 months. A latency period was allowed and all surviving benzotrichloride-treated mice were sacrificed at 13.3 months and the controls at 18.7 months. Mortality at termination was 20% in the controls compared with 35% in the treated group. The incidences of skin carcinomas and lung adenoma or lung carcinoma are presented in Table 5-2. Nineteen other tumors, attributed to licking, were observed in the lips, tongue, esophagus, forestomach and glandular stomach of the treated mice.

5.1.2. Human Studies. No case reports or epidemiological studies involving exposure to benzotrichloride alone were available. Sakabe et al. (1976), however, reported four cases of cancer among 41 workers employed from 1954-1972 in the manufacture of benzoyl chloride, a process in which

benzotrichloride is a reagent. One case was of maxillary malignant lymphoma and one was diagnosed as squamous cell carcinoma of the bronchus. These cases were not used in the epidemiological analysis. Two of the cases were of lung cancer, which were used in the epidemiological analysis (Table 5-3). These individuals were in their mid-forties, were smokers and were employed for 6-15 years during which time they had also been exposed to toluene, benzal chloride and benzyl chloride. Latency periods of 6-18 years elapsed before the lung cancers were diagnosed. Compared with the Japanese national rates for lung cancer, the number of expected tumors in the cohort of 41 exposed workers was 0.06 (relative risk = 33.3; $p=0.002$) and the numbers of expected tumors in the cohort of 147 total workers (exposed and nonexposed) was 0.22 (relative risk = 9.1; $p=0.02$). Sakabe et al. (1976) considered that the four cases of cancer were related to exposure to one or more of the chemicals used in the benzoyl chloride production process. This conclusion is supported by Sakabe and Fukuda (1977), who found two additional cases of lung cancer among workers engaged in benzoyl chloride and benzoyl peroxide production at another small plant. No epidemiological analysis was made by Sakabe and Fukuda (1977). Except for length of employment these studies provided no qualitative or quantitative evidence of exposure to benzoyl chloride. However, in their evaluation IARC (1982b) concluded that data are inadequate to evaluate the carcinogenicity of benzotrichloride alone, but that the data do provide limited evidence that a carcinogenic risk to humans is represented by employment in benzoyl chloride production.

Sorahan et al. (1983) conducted an epidemiological study of workers exposed to mixed chlorinated toluenes. The total cohort consisted of 953 workers employed at a British organic chemicals factory at sometime from January, 1961 to December, 1970; 163 of the workers had been exposed to

TABLE 5-3
Lung Cancer in Workers Employed in Benzoyl Chloride Production^a

Exposure Route	Size of Exposed Population	Size of Control Population	Sex	Level of Exposure	Duration of Exposure (years)	Tumor Type	Number of Tumors Observed	Number of Tumors Expected	Relative Risk (p value) ^b
Occupational	41 (benzoyl chloride workers only)	NR (Japanese nationals)	M	NR	6-15	histologically undefined	2	0.06	33.3 (0.002)
Occupational	147 (all workers)	NR (Japanese nationals)	M/F	NR	6-15	histologically undefined	2	0.22	9.1 (0.02)

QUALITY OF EVIDENCE

Strengths of Study: Study attempts to relate observed values with expected values derived from the general population (Japanese nationals)

Weaknesses of Study: Both individuals with cancer were smokers and were exposed to other chemicals, including benzal chloride and benzyl chloride. A third case of lung cancer (squamous cell carcinoma of the bronchus) was not included in the analysis.

Overall Adequacy: Limited

Comments: The association between lung cancer and benzoyl chloride production is supported by two cases of lung cancer in men employed in benzoyl chloride production in another plant (Fukuda and Sakabe, 1977).

^aSource: Sakabe et al., 1976

^bThe p values were obtained from IARC (1982a).

NR = Not reported

chlorinated toluenes. Of the 25 deaths in this group, 5 were from cancer of the digestive system and 5 were from cancer of the respiratory system. All 10 cancer deaths occurred in workers whose first year of employment occurred between 1923 and 1960. According to the mortality rates for England and Wales, the expected number of all cancers was 3.98 (SMR = 251; $p < 0.01$), of respiratory cancers was 1.78 (SMR = 281; $p < 0.05$) and of digestive system cancers was 1.24 (SMR = 403; $p < 0.05$) (Table 5-4). Because of the association of cancers with benzotrichloride exposure in animal studies, Sorahan et al. (1983) considered benzotrichloride to be the most likely causative chemical among the possible chlorinated toluenes. Workroom atmospheric levels of benzotrichloride were < 1 ppm in the mid-1970s, while prior to 1965, the levels were estimated to be ≥ 10 ppm. However, because of methodological inadequacies (such as qualitative and quantitative evidence of exposure, absence of control data and evaluations of associated confounding factors) the human data are considered inadequate to determine the carcinogenic potential of benzotrichloride.

5.2. MUTAGENICITY

Results of mutagenicity tests of benzotrichloride are equivocal (Table 5-5). Yasuo et al. (1978) reported his findings in the rec assay using Bacillus subtilis strains H17 and M45 and in reverse mutation assays in Escherichia coli WP2 hcr and Salmonella typhimurium TA98, TA100 and TA1535 with, but not without, metabolic activation. Benzotrichloride was positive for mutagenicity in the rec assay and was highly positive in E. coli and S. typhimurium in the reversion assay with metabolic activation. Without metabolic activation, however, benzotrichloride was only weakly positive in the latter assay. Jagannath (1978), however, found negative results for reverse mutation in five strains of S. typhimurium and for forward mutation in Saccharomyces cerevisiae strain D4 with and without metabolic activation.

TABLE 5-4

Digestive and Respiratory Cancers in Occupationally-Exposed Humans*

Size of Exposed Population	Size of Control Population	Sex	Level of Exposure	Duration of Exposure	Target Organ	Tumor Type	Number of Cases Observed	Number of Cases Expected	Relative Risk (p value)
163	England and Wales mortality rates	M	1-10 ppm	6 months to >40 years	digestive system	cancer	5	1.24	SMR=403 (p<0.05)
					respiratory system	cancer	5	1.78	SMR=281 (p<0.05)
					digestive and respiratory system	cancer	10	3.98	SMR=251 (p<0.01)

QUALITY OF EVIDENCE

Strengths of Study: Time- and age-specific comparison between the exposed group and national mortality rates was conducted. The increase in tumors of the digestive and respiratory systems are corroborative with the tumorigenesis seen in mice.

Weaknesses of Study: Exposure was to several chlorinated toluene compounds so that benzotrchloride cannot be positively correlated to the increased cancer mortality. The number of deaths is small.

Overall Adequacy: Limited

*Source: Sorahan et al., 1983

TABLE 5-5
Mutagenicity Testing of Benzotrichloride*

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Rec assay	<i>Bacillus subtilis</i> H17 (Rec ⁺) M45 (Rec ⁻)	plate incorporation	1.5-3.6 μ mol/disk	none	+	MC	Yasuo et al., 1978
Reverse mutation	<i>Escherichia coli</i> WP2 hcr, B/r (hcr ⁺)	plate incorporation	0-1.0 μ mol/plate	±S-9	±	Relatively highly mutagenic in WP2 hcr in the presence of S-9	Yasuo et al., 1978
Reverse mutation	<i>Salmonella typhimurium</i> TA100, TA98, TA1535	plate incorporation	0-1.0 μ mol/plate	±S-9	±	Mutagenic in all strains in the presence of S-9	Yasuo et al., 1978
Reverse mutation	<i>S. typhimurium</i> TA100, TA98, TA1535, TA1537, TA1538	plate incorporation	0-10 μ t/plate	±S-9	=	The compound was toxic at the 5 and 10 μ t/plate dose levels	Jagannath, 1978
Forward mutation	<i>Saccharomyces cerevisiae</i> D4	plate incorporation	0-10 μ t/plate	±S-9	=	MC	Jagannath, 1978

*Source: U.S. EPA, 1982

The differences may be due to different concentrations (1.0 μ mol ~195 μ g, 10 μ l ~13.8 μ g), but Jagannath (1978), who used the lower concentrations, found that benzotrichloride was toxic to the cells at 5 and 10 μ l/plate

5.3. TERATOGENICITY

Ruddick et al. (1982) administered benzotrichloride by gavage to pregnant rats (strain unspecified) on days 6-15 of gestation at dose levels of 0, 12.5, 25 or 50 mg/kg/day. Maternal weight gain, changes in weights or organs, hematology, microscopic examinations along with several biochemical parameters were used to evaluate maternal toxicity. Litter size, fetal weight, deciduoma, skeletal and visceral examinations were included in the fetotoxic evaluations. At the two high dosage exposure levels the maternal weight gain was significantly reduced; depression of fetal weight gain was observed at all dosage levels. Skeletal anomalies were observed at unspecified dosages. No other teratogenic effects were reported. The high dose (50 mg/kg) caused significant alterations in some (not reported) clinical, hematological and organ weights of the exposed dams. Despite lack of details of some of the pertinent parameters in this abstract, the compound appeared to be toxic to both the mother and the developing fetus.

5.4. REPRODUCTIVE EFFECTS

Nair (1980) treated New Zealand white rabbits dermally with 0, 50, 100 or 200 mg/kg/day benzotrichloride, 5 days/week for 3 weeks. At 100 and 200 mg/kg/day, there were increased incidences of multinucleated giant cells in the seminiferous tubules and degeneration of the seminiferous tubules in the testes of the males.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

In the oral carcinogenicity study by Fukuda et al. (1978) (see Section 5.1.), groups of 40 female ICR mice were treated by gavage with benzotrichloride at 0.043, 0.17, 0.7 or 2.7 mg/mouse, 2 days/week for 25 weeks. The mice were observed for 18 months following the start of the experiment. In the highest and next to highest dose groups, 50% mortality was reached at 6.5 and 16.5 months, respectively. The lower dose groups did not reach 50% mortality by 18 months. Further details regarding mortality were not provided. In addition to the increased incidences of squamous cell carcinoma of the forestomach (see Section 5.1.), other proliferative lesions in the forestomach and glandular stomach were observed, even in mice that had no tumors. The doses at which these lesions occurred, however, were not specified.

Chu et al. (1984) treated groups of 10 male and 10 female weanling Sprague-Dawley rats with benzotrichloride at dietary levels of 0, 0.5, 5, 50 or 500 ppm for 28 days. There were no clinical signs of toxicity, no deaths and no effects on food consumption, body weight gain, organ weights or hematological parameters. Serum levels of sorbitol dehydrogenase were increased significantly ($p < 0.05$) in males treated at ≥ 5 ppm, compared with controls. Histological examination of major organs revealed dose-related increased incidences and severity of lesions in the liver, kidneys and thyroid. Liver lesions included pyknosis, hepatocellular necrosis and cytoplasmic vacuolization in the portal areas. Kidney lesions included accumulation of eosinophilic inclusions in epithelial cells of the proximal tubules, focal granular adhesions and interstitial scarring. Thyroid lesions consisted of reduced follicular size, and papillary proliferation and vacuolization in epithelial cells. Columnar and thickened epithelial cells with collapsed follicles were also observed.

Iakemoto et al. (1978) exposed 32 five-week-old ICR female mice to vapors of benzotrichloride at 6.8 ppm (54 mg/m³), 2 days/week for 5 months, followed by 5 months of observation. There were no controls. In addition to the tumors observed in the exposed mice (see Section 5.1.), epithelial proliferation of the trachea, bronchus and bronchioli, hypertrophy of the thymus, lymph nodes and spleen, mild keratocyte proliferation of the stomach and inflammation of the spleen were observed among the "majority" of treated mice. Mortality was high; 17/32 mice died before the end of the study. Inflammation and hypertrophy of lymph nodes, liver, spleen and kidney and proliferative lesions of the respiratory tract along with lung tumors also occurred at high incidences in the female ICR mice (n=37) exposed by inhalation to 1.6 ppm (12.8 mg/m³), 2 days/week for 12 months, followed by 12 or 15 months of observation (Yoshimura et al., 1979) (see Section 5.1.). There were no controls. Mortality was high; 10 mice died during the 12 months of exposure and 8 mice died during the observation period.

Histopathological lesions of the respiratory tract were observed in rats in a subchronic inhalation study (Levin, 1981). Groups of 10 male and 10 female rats of unspecified strain were exposed by inhalation to benzotrichloride at 0, 5.1, 48.2 or 460 µg/l (0, 5.1, 48.2 or 460 mg/m³), 6 hours/day, 5 days/week for 4 weeks. At the highest exposure level, all the rats had marked dyspnea and died or were killed in extremis within the first week. At 48.2 mg/m³, the rats had decreased body weight gain from the first to the fourth week and slight dyspnea after 4 weeks. Gross and histological examination revealed lung congestion, inflammatory cell infiltration, degeneration, desquamation and epithelial ulceration in the bronchi and bronchioles, and inflammatory cell infiltration or squamous metaplasia

of the epithelial cells in the nasal turbinate and trachea. No effects were observed at 5.1 mg/m³.

In a subchronic dermal study, Nair (1980) applied benzotrichloride to the shaved backs of New Zealand white rabbits at dose levels of 0, 50, 100, and 200 mg/kg/day. Groups of four males and four females (two/sex intact, and two/sex abraded) were treated 5 days/week for 3 weeks, followed by 3 weeks of observation. One 200 mg/kg male died during the study period. No treatment-related effects on general behavior, body weight, blood measurements and urinalyses were reported. Moderate to severe erythema, edema, atonia, desquamation, coriaceousness and fissuring were observed in most rabbits at all doses; the severity increased with dose. Eschar formation, exfoliation and necrosis were also observed among all dosage groups, while blanching occurred at 200 mg/kg.

Microscopic skin lesions occurred at all dose levels and included inflammatory and necrotic changes, acanthosis, hyperkeratosis and ulceration. In the liver, the incidence of portal inflammatory cell infiltrate was increased in all treated groups and the incidence of bile duct proliferation was increased in the 200 mg/kg group. Also, an increased dose-related incidence of multinucleated giant cells in the seminiferous tubules and degeneration of seminiferous tubules in the testes of rabbits from the 100 and 200 mg/kg groups were reported.

5.6. OTHER RELEVANT INFORMATION

The oral LD₅₀ values with 95% confidence limits were determined to be 807 (692-941) mg/kg in mice (Dean, 1978) and 736 (616-878) mg/kg in rats (Dean, 1979). The LC₅₀ value for 1-hour exposure of rats to benzotrichloride is 8.39 mg/l (8390 mg/m³) with 95% confidence limits of 7810 to 3970 mg/m³ (Cavender, 1979). The dermal LD₅₀ with 95% confidence limits in rabbits is 4000 (2000-8000) mg/kg (Dean, 1979).

5.7. SUMMARY

Oral administration of benzotrichloride to female mice at doses of 0, 0.043, 0.17, 0.7 or 2.7 mg/mouse, 2 days/week for 25 weeks, followed by observation for ~1 year caused dose-related increases in the incidence of squamous-cell carcinomas of the forestomach, adenocarcinomas of the lung and thymomas (Fukuda et al., 1978). Inhalation exposure of female mice to 1.6 ppm (12.8 mg/m³) benzotrichloride for 30 minutes, twice weekly for 12 months followed by an observation period of 12-15 months, resulted in a high incidence of cancerous lesions in the lungs. Similar results were obtained by Takemoto et al. (1978) who exposed female rats by inhalation to 6.8 ppm (54 mg/m³) for 30 minutes, twice weekly for 5 months, followed by a 5-month observation period. No control groups were reported in these studies. Fukuda et al. (1981) found that skin and lung carcinoma were produced in female mice by dermal application; upper-digestive tract tumors were also produced, which was possibly due to licking of the skin while grooming.

In humans, data on the carcinogenic effects of benzotrichloride exposure alone are not available. Increased incidence of digestive and respiratory cancers were found among workers exposed to benzotrichloride, benzyl chloride, benzal chloride and toluene in the manufacturing of benzoyl chloride and other chlorinated toluenes (Sakabe et al., 1976; Sakabe and Fukuda, 1977; Scrahan et al., 1983).

Results of mutagenicity testing of benzotrichloride in bacterial systems are equivocal (see Table 5-4). Positive results were obtained in a rec assay in Bacillus subtilis and in reverse mutation assays in Escherichia coli and Salmonella typhimurium when a metabolic activation system was

present (Yasuo et al., 1978). Negative results were found for reverse mutation in S. typhimurium and for forward mutation in Saccharomyces cerevisiae in the absence and presence of metabolic activation (Jagannath, 1978).

Gavage administration of benzotrichloride to pregnant rats on days 6-15 of gestation at dose levels of 0, 12.5, 25 or 50 mg/kg/day resulted in reduced mean fetal weight at all doses and skeletal anomalies at unspecified doses (Ruddick et al., 1982). At 50 mg/kg/day, there were increased numbers of resorptions and reduced litter sizes.

Increased mortality was observed in female mice treated by gavage with 0.7 or 2.7 mg/mouse, 2 days/week for 25 weeks (Fukuda et al., 1978). In addition to increased incidences of stomach tumors, other proliferative stomach lesions were observed at unspecified doses. Dietary treatment of rats for 28 days resulted in increased serum levels of sorbitol dehydrogenase and dose-related increased incidence and severity of lesions in the liver, kidney and thyroid at ≥ 0.5 ppm (Chu et al., 1984). The oral LD_{50} of benzotrichloride is 807 mg/kg for mice (Dean, 1978) and 736 mg/kg for rats (Dean, 1979).

High mortality was observed in female mice exposed by inhalation to 1.6 ppm (12.8 mg/m³), 2 days/week for 12 months (Yoshimura et al., 1979) or to 6.8 ppm (54 mg/m³), 2 days/week for 5 months (Takemoto et al., 1978). In addition to the high incidences of lung tumors in these mice, other proliferative lesions were observed in the respiratory tract. There were also inflammation and hypertrophy of lymph nodes, liver, spleen and kidneys. Lung congestion, inflammatory cell infiltration, degeneration, desquamation, ulceration and squamous metaplasia were observed in the respiratory tract of rats exposed by inhalation to 48.2 or 460 mg/m³, 6 hours/day, 5 days/week for 4 weeks (Levin, 1981). Rats exposed to 48.2 mg/m³ had reduced body

weight and dyspnea, while all rats exposed to 460 mg/m³ had severe dyspnea and died during the first week. The 1-hour inhalation LC₅₀ of benzotri-chloride for rats is 8390 mg/m³ (Cavender, 1979).

6. AQUATIC TOXICITY

6.1. ACUTE

The limited information concerning the effects of benzotrichloride on aquatic biota is presented in Table 6-1. Benzotrichloride is relatively nontoxic to fish, having a 48-hour LC_{50} of 4140 mg/l for the golden orfe, Leuciscus idus, the only species tested (Juhnke and Luedemann, 1978). Since this reported LC_{50} is larger than solubility (see Section 1.2.) and since benzotrichloride hydrolyzes rapidly in water, the solubility of the LC_{50} dose is questionable. Apparently, benzotrichloride is also relatively nontoxic to invertebrates, with mosquito larvae, Anopheles quadrimaculatus, and Daphnia magna having LC_{50} values greater than the highest concentrations tested (10 and 100 mg/l, respectively) (Bringmann and Kuehn, 1977; Deonier et al., 1946). Sublethal effects have been reported in some species, with Daphnia magna having an EC_{50} for immobilization of 50 mg/l (Bringmann and Kuehn, 1982) and three protozoans having toxicity thresholds of 27 to >80 mg/l (Bringmann and Kuehn, 1981).

6.2. CHRONIC

Pertinent data regarding the chronic toxicity of benzotrichloride to aquatic organisms could not be located in the available literature as cited in the Appendix.

6.3. PLANTS

Bringmann and Kuehn (1978, 1980) reported that toxicity thresholds for the inhibition of cell multiplication were 34 mg/l for the blue-green alga, Microcystis aeruginosa, and >100 mg/l for the bacterium, Pseudomonas putida, and the green alga, Scenedesmus quadricauda.

6.4. RESIDUE

Pertinent data regarding benzotrichloride residue in aquatic biota could not be located in the available literature as cited in the Appendix.

TABLE 6-1
Aquatic Toxicity Data for Benzotrichloride

Species	Concentration (mg/l)	Response	Reference
Fish Golden orfe (<u>Leuciscus idus</u>)	2480 4140 8280	48-hour LC ₅₀ 48-hour LC ₅₀ 48-hour LC ₁₀₀	Juhnke and Luedemann, 1978
Insects Mosquito (<u>Anopheles quadrimaculatus</u>)	>10	lowest concentration toxic to 4th instar larvae	Deonier et al., 1946
Crustaceans Water flea (<u>Daphnia magna</u>)	42 50 56 >100	24-hour EC ₅₀ , immobilization 24-hour EC ₅₀ , immobilization 24-hour EC ₁₀₀ , immobilization 24-hour LC ₅₀	Bringmann and Kuehn, 1982 Bringmann and Kuehn, 1977
Protozoa Flagellate (<u>Entosiphon sulcatum</u>)	56	toxicity threshold, inhibition of cell multiplication	Bringmann and Kuehn, 1981
Flagellate (<u>Chlomonas paramecium</u>)	27	toxicity threshold, inhibition of cell multiplication	Bringmann and Kuehn, 1981
Ciliate (<u>Uronema parduczi</u>)	>80	toxicity threshold, inhibition of cell multiplication	Bringmann and Kuehn, 1981
Bacteria <u>Pseudomonas putida</u>	>100	toxicity threshold, inhibition of cell multiplication	Bringmann and Kuehn, 1980
Blue-green algae <u>Microcystis aeruginosa</u>	34	toxicity threshold, inhibition of cell multiplication	Bringmann and Kuehn, 1978
Algae <u>Scenedesmus quadricauda</u>	>100	toxicity threshold, inhibition of cell multiplication	Bringmann and Kuehn, 1978

6.5. SUMMARY

Little information is available concerning the toxicity of benzotri-chloride to aquatic organisms. It is relatively nontoxic to fish, having a 48-hour LC_{50} of ~4 g/l to the only species tested, Leuciscus idus (Juhnke and Luedemann, 1978). However, since the solubility of the compound is greater than the reported solubility and since the compound hydrolyzes rapidly in water, the validity of this LC_{50} is questionable. In other bioassays, LC_{50} values could not be determined because the concentrations tested were not high enough to cause significant mortality. Sublethal effects were observed in other species, with the most sensitive effect being the toxic threshold for inhibition of cell multiplication in the protozoan, Chilomonas paramecium, at 27 mg/l (Bringmann and Kuehn, 1981, 1982).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Pertinent guidelines and standards, including EPA ambient water and air quality criteria, drinking water standards, FAO/WHO ADIs, EPA or FDA tolerances for raw agricultural commodities or food and ACGIH, NIOSH or OSHA occupational exposure limits could not be located in the available literature as cited in the Appendix.

7.2. AQUATIC

Pertinent data regarding aquatic guidelines and standards for benzonitrile could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Oral administration of benzotrichloride to female mice at 0, 0.043, 0.1, 0.17, 0.7 or 2.7 mg/mouse, 2 days/week (0, 0.4, 1.6, 6.7, 25.7 mg/kg/day, using 0.03 kg as the mouse weight) for 25 weeks followed by 78 weeks of observation resulted in dose-related, significantly increased incidences of squamous cell carcinoma of the forestomach at ≥ 6.7 mg/kg/day and of lung adenoma/adenocarcinoma at ≥ 1.6 mg/kg/day and a significantly increased incidence of thymoma at 25.7 mg/kg/day (Fukuda et al., 1978). Inhalation exposure of female mice to 1.6 ppm (12.8 mg/m³) for 30 minutes, 2 days/week for 12 months followed by an observation period of 12-15 months, resulted in a high incidence of lung tumors (Yoshimura et al., 1979). Similar results were obtained in female mice exposed by inhalation to 6.8 ppm (54 mg/m³) for 30 minutes, twice weekly for 5 months, followed by 5 months of observation (Takemoto et al., 1978). No controls were used in these studies. Fukuda et al. (1981) found increased incidences of skin carcinoma, lung adenoma/carcinoma and lymphoma of the thymus in female mice treated dermally with benzotrichloride in benzene compared with benzene-treated controls. In humans, data regarding the carcinogenic effect of benzotrichloride exposure alone were not available. Increased incidences of digestive and respiratory cancers were found among workers exposed to benzotrichloride, benzal chloride, benzyl chloride and toluene in the manufacture of benzoyl chloride and other chlorinated toluenes (Sakabe et al., 1976; Sakabe and Fukuda, 1977; Sorahan et al., 1983).

Results of mutagenicity tests of benzotrichloride in bacterial systems are equivocal. Yasuo et al. (1978) obtained positive results in a rec assay in Bacillus subtilis, in reverse mutation assays in Escherichia coli and

Salmonella typhimurium in the presence of metabolic activation. Jagannath (1978), however, found negative results for reverse mutation in S. typhimurium and for forward mutation in Saccharomyces cerevisiae in the presence and absence of metabolic activation.

Gavage administration of benzotrichloride to pregnant rats on days 6-15 of gestation at 0, 12.5, 25 or 50 mg/kg/day resulted in reduced mean fetal weight at all doses, skeletal anomalies at unspecified doses, and increased numbers of resorptions and reduced litter sizes at 50 mg/kg/day.

Increased mortality was observed in female mice treated by gavage with 0.7 or 2.7 mg/mouse, 2 days/week for 25 weeks (Fukuda et al., 1978). In addition to increased incidences of stomach tumors, other proliferative stomach lesions were observed at unspecified doses. Dietary treatment of rats for 28 days resulted in increased serum levels of sorbitol dehydrogenase and dose-related increased incidence and severity of lesions in the liver, kidneys and thyroid at ≥ 0.5 ppm (Chu et al., 1984).

High mortality was observed in female mice exposed by inhalation to 1.6 ppm (12.8 mg/m³), 2 days/week for 12 months (Yoshimura et al., 1979) or to 6.8 ppm (54 mg/m³), 2 days/week for 5 months (Takemoto et al., 1978). In addition to the high incidences of lung tumors in these mice, other proliferative lesions were observed in the respiratory tract. There were also inflammation and hypertrophy of lymph nodes, liver, spleen and kidneys. Lung congestion, inflammatory cell infiltration, degeneration, desquamation, ulceration and squamous metaplasia were observed in the respiratory tract of rats exposed by inhalation to 48.2 or 460 mg/m³, 6 hours/day, 5 days/week for 4 weeks (Levin, 1981). Rats exposed to 48.2 mg/m³ had reduced body weight and dyspnea, while all rats exposed to 460 mg/m³ had severe dyspnea and died during the first week.

Because the results of the Fukuda et al. (1978) bioassay indicated a compound-related increased incidence of squamous cell carcinoma in the forestomach, adenocarcinomas and adenomas of the lungs, and thymomas in the thymus of the dosed female mice (see Table 5-1), it is appropriate to derive a carcinogenic potency factor (q_1^*) for humans for benzotrichloride. Because Fukuda et al. (1978) did not provide individual mouse pathology data, it is not possible to determine if more than one tumor type occurred in the same mouse. Therefore, it is not possible to pool the tumor incidence data; separate q_1^* determinations are made for the squamous cell carcinomas of the forestomach, for adenocarcinomas of the lungs and for the thymomas (Tables 8-1, 8-2 and 8-3). The transformed doses were calculated by dividing the experimental doses by the reference mouse body weight of 0.03 kg and by multiplying by 2 days/7 days. This calculation results in the doses that appear in Table 5-1. To obtain the doses that appear in Tables 8-1 to 8-3, a further correction is made by multiplying by $1e/Le$. The unadjusted values for q_1^* were calculated using the computerized multistage model, GLOBAL 82, developed by Howe and Crump (1982). The human q_1^* values were calculated by multiplying the unadjusted value by the cube root of the ratio of the reference human body weight (70 kg) to the mouse body weight. Since the length of the experiment in mice was less than the lifespan of mice, the unadjusted values were further corrected by $(L/Le)^3$.

As seen from Tables 8-1, 8-2 and 8-3, the dose-response data for tumor types did not adequately fit the model; therefore, the highest dose was dropped, and the q_1^* was recalculated based on the tumor incidence data at the lower doses. Since the q_1^* of $12.63 \text{ (mg/kg/day)}^{-1}$ resulting from the data on adenocarcinomas of the lungs is higher than that generated from the data for tumors in the forestomach and thymus, it is recommended for

TABLE 8-1

Cancer Data Sheet for Derivation of q_1^*

Compound: benzotrichloride

Reference: Fukuda et al., 1978

Species, Strain, Sex: mouse, ICR, female

Body weight: 0.03 kg (assumed)

Length of exposure (t_e) = 25 weeksLength of experiment (L_e) = 78 weeksLifespan of animal (L) = 104 weeks

Tumor site and type: forestomach, squamous-cell carcinoma

Route, vehicle: gavage, sesame oil

Experimental Doses or Exposures (mg/mouse)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Examined
0.0	0.0	0/35
0.043	0.13	0/37
0.17	0.52	2/38
0.7	2.12	22/40
2.7	8.24	24/35

NOTE: Goodness of fit using all five doses was not adequate; therefore, high dose was dropped from the derivation of q_1^* .

Unadjusted q_1^* from study = 1.9080801×10^{-1} (mg/kg/day) $^{-1}$

Human q_1^* = 5.9989 (mg/kg/day) $^{-1}$

TABLE 8-2

Cancer Data Sheet for Derivation of q_1^*

Compound: benzotrachloride

Reference: Fukuda et al., 1978

Species, Strain, Sex: mouse, ICR, female

Body weight: 0.03 kg (assumed)

Length of exposure (t_e) = 25 weeksLength of experiment (t_e) = 78 weeksLifespan of animal (L) = 104 weeks

Tumor site and type: adenocarcinomas of the lungs

Route, vehicle: gavage, sesame oil

Experimental Doses or Exposures (mg/mouse)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Examined
0.0	0.0	0/35
0.043	0.13	1/37
0.17	0.52	9/38
0.7	2.12	16/40
2.7	8.24	10/35

Note: Goodness of fit using all five doses was not adequate; therefore, high dose was dropped from the derivation of q_1^*

Unadjusted q_1^* from study = 4.01895×10^{-1} (mg/kg/day) $^{-1}$

Human q_1^* = 12.6354 (mg/kg/day) $^{-1}$

TABLE 8-3

Cancer Data Sheet for Derivation of q_1^*

Compound: benzotrichloride
 Reference: Fukuda et al., 1978
 Species, Strain, Sex: mouse, ICR, female
 Body weight: 0.03 kg (assumed)
 Length of exposure (t_e) = 25 weeks
 Length of experiment (t_e) = 78 weeks
 Lifespan of animal (L) = 104 weeks
 Tumor site and type: thymus, thymoma
 Route, vehicle: gavage, sesame oil

Experimental Doses or Exposures (mg/mouse)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Examined
0.0	0.0	0/35
0.043	0.13	0/37
0.17	0.52	1/38
0.7	2.12	2/40
2.7	8.24	7/35

Note: Goodness of fit using all five doses was not adequate; therefore, high dose was dropped from the derivation of q_1^*

Unadjusted q_1^* from study = 4.42055×10^{-2} (mg/kg/day) $^{-1}$

Human q_1^* = 1.3900 (mg/kg/day) $^{-1}$

estimating the increased lifetime risk of human exposure to benzotrichloride. The concentrations in water associated with increased risk levels of 10^{-5} , 10^{-6} and 10^{-7} are 2.8×10^{-5} , 2.8×10^{-6} and 2.8×10^{-7} mg/l, respectively. Benzotrichloride, however, hydrolyzes rapidly in water to benzoic acid; therefore, it probably will not be recovered in water supplies.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The subchronic and chronic studies of benzotrichloride have been reviewed in Section 5.5. In addition, a teratogenicity study, which was discussed in Section 5.3., was also available. These studies are summarized in Table 9-1.

Increased mortality of mice was observed in the oral study by Fukuda et al. (1978) at ≥ 6.7 mg/kg/day and in the inhalation studies of Takemoto et al. (1978) and Yoshimura et al. (1979) at ≥ 0.10 mg/kg/day. Although some of the mice that died early had squamous cell carcinomas of the forestomach and adenomas and carcinomas of the lung, it is uncertain if the deaths were tumor-related. It is, therefore, appropriate to calculate CSs for increased mortality. Histopathological lesions in the stomach, respiratory organs, thymus, spleen, liver and kidneys were also observed in mice at doses that resulted in increased mortality. Because these effects are less severe than early death, it is not necessary to calculate CSs for histopathological lesions in mice. The lowest dose at which high mortality of mice was observed was 0.10 mg/kg/day in the inhalation study by Yoshimura et al. (1979). The MED of 0.53 mg/day (Table 9-2) was calculated by multiplying the transformed animal dose of 0.1 mg/kg/day by the cube root of the ratio of the mouse body weight (0.03 kg) to the reference human body weight of 70 kg and by 70 kg to express the MED in mg/day. The MED corresponds to an RV_d of 5.9. Increased mortality warrants an RV_e of 10. Multiplying the RV_d by the RV_e results in a CS of 59, which corresponds to an RQ of 10 (see Table 9-2).

TABLE 9-1

Toxicity Summary for Benzo(a)pyrene

Route	Species/ Strain	Sex	No. at Start	Average Weight (kg) (assumed)	Vehicle/ Physical State	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Response	Reference
Oral/ gavage	mouse/ICR	♂	40/group	0.03	sesame oil	NR	0.043, 0.17, 0.7 or 2.7 mg/mouse, 2 days/week for 25 weeks and observed for 78 weeks	0.4, 1.6, 6.7 or 25.7 ^a	Increased mortality at >6.7 mg/kg/day; prolifer- ative lesions in fore- stomach and glandular stomach at unspecified doses; increased inci- dences of stomach and lung tumors at ≥1.6 mg/kg/day	Fukuda et al., 1978
Oral	rat/ Sprague- Dawley	M, F	10/sex/ group	0.09 ^b	diet	98%	0.5, 5, 50 or 500 ppm for 28 days	0.05, 0.5, 5 or 50 ^c	Increased levels of sorbitol dehydrogenase at ≥0.5 mg/kg/day; dose- related increased inci- dence and severity of liver, kidney and thyroid at unspecified doses	Chu et al., 1984
Oral/ gavage	rat/NR	F	NR	0.35	NR	NR	12.5, 25 or 50 mg/kg/day on days 6-15 of gestation	12.5, 25 or 50	Reduced fetal body weight at all doses, in- creased resorptions and reduced litter size at 50 mg/kg/day; skeletal anomalies at unspecified dose	Ruddick et al., 1982
Inhalation	mouse/ICR	♂	32	0.03	air/vapor	NR	6.8 ppm (54 mg/m ³), 30 minutes/day, 2 days/week, for 5 months and observed for 5 months	0.42 ^d	High mortality, prolifer- ative lesions in respira- tory tract, high inci- dences of lung tumors; hypertrophy of thymus, lymph nodes and spleen; keratinocyte proliferation in stomach (no controls were used)	Takemoto et al., 1978

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	No. at Start	Average Weight (kg) (assumed)	Vehicle/ Physical State	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Response	Reference
Inhalation	mouse/ICR	F	37	0.03	air/vapor	NR	1.6 ppm (12.8 mg/m ³), 30 minutes/day, 2 days/week, for 12 months and observed for 12-15 months	0.10 ^d	High mortality, inflammation and hypertrophy of lymph nodes, liver, spleen and kidney; proliferative lesions of the respiratory tract; high incidences of lung tumors (no controls were used)	Yoshimura et al., 1979
Inhalation	rat/NR	M,f	10/sex/ group	0.35	air/vapor	NR	5.1, 48.2 or 460 µg/L (mg/m ³), 6 hours/day, 5 days/week for 4 weeks	0.50, 5.48 or 52.3 ^e	Decreased body weight gain at 5.48 mg/kg/day; all rats at 52.3 mg/kg/day died during first week; lung congestion, inflammatory cell infiltration, degeneration, desquamation, ulceration in bronchi and bronchioles; inflammatory cell infiltration and/or squamous metaplasia of epithelial cells of nasal turbinate and trachea at 5.48 and 52.3 mg/kg/day	Levin, 1981

^aDose calculated by dividing mg/mouse by the reference body weight of the mouse (0.03 kg) and by multiplying by 2 days/7 days.

^bThe rats weighed 0.06 kg at the start of exposure. If the rats gained -0.02 kg/day, the end weight would be -0.116 kg, and the average weight would be -0.09 kg.

^cApproximate doses supplied by Chu et al. (1984)

^dDose calculated by multiplying the exposure concentration by 0.5 hours/24 hours, by 2 days/7 days, by the mouse inhalation rate (0.039 m³/day) and by dividing by the mouse body weight.

^eDose calculated by multiplying the exposure concentration by 6 hours/24 hours, by 5 days/7 days, by the rat inhalation rate (0.223 m³/day) and by dividing by the rat body weight (0.35 kg).

TABLE 9-2
Composite Scores for Benzotrithloride

Route	Species	Animal Dose (mg/kg/day)	Chronic Human MLD (mg/day)	RV _d	Effect	RV _e	CS	RQ	Reference
Oral	rat/f	12.5	150	2.2	Reduced fetal body weight, skeletal anomalies	8	17.6	1000	Ruddick et al., 1982
Oral	rat	0.05	0.04*	7.6	Mild lesions in kidney, liver and thyroid	5	38	100	Chu et al., 1984
Inhalation	mouse	0.10	0.53	5.9	Increased mortality	10	59	10	Yoshimura et al., 1979
Inhalation	rat	5.48	6.6*	4.3	Histological lesions in respiratory tract including degeneration, ulceration, metaplasia	6	25.0	100	Levin, 1981

*Uncertainty factor of 10 was applied

The only oral studies in rats were the 28-day dietary study by Chu et al. (1984) and the teratology study by Ruddick et al. (1982). In the study by Chu et al. (1984) there were dose-related increased incidences and severity of liver, kidney and thyroid lesions of rats at unspecified doses. The lesions were considered mild even at the highest dose and included pyknosis, occasional hepatocellular necrosis, and cytoplasmic vacuolization in the liver, eosinophilic infiltrations in renal tubules, glomerular adhesions and interstitial scarring in the kidney and follicular changes in the thyroid. If these lesions occurred with minimal severity at the lowest dose, the highest RV_e that can be assigned is 5. Multiplying the lowest dose of 0.05 mg/kg/day by the cube root of the ratio of the average body weight of the rats in the Chu et al. (1984) study (0.09 kg) to the reference human body weight (70 kg) and by 70 kg and dividing by 10 to approximate chronic exposure results in an MED of 0.04 mg/day. This MED corresponds to an RV_d of 7.6. Multiplying the RV_d by the RV_e results in a CS of 38, which corresponds to an RQ of 100.

Ruddick et al. (1982) found fetotoxic effects in the offspring of rats treated orally with benzotrichloride during gestation. Because any signs of fetotoxicity warrant an RV_e of 8, it is appropriate to use 12.5 mg/kg/day, which resulted in reduced body weight of fetuses. The MED of 150 mg/day was calculated by multiplying the animal dose by the cube root of the ratio of the rat body weight (0.35 kg) to the human body weight and by 70 kg. An uncertainty factor of 10 is not necessary because the exposure is chronic to the life of the fetus. The MED corresponds to an RV_d of 2.2, the CS is 17.6, which corresponds to an RQ of 1000.

The only inhalation study in rats was the 4-week study reported by Levin (1981). At 5.48 mg/kg/day, there was reduced body weight gain and histopathological lesions in the respiratory tract (see Table 9-1). The highest RV_e that can be assigned to these effects is 6. The MED of 6.6 mg/day was calculated as described using a rat body weight of 0.35 kg. In addition, an uncertainty factor of 10 was used to approximate chronic exposure. Multiplying the corresponding RV_e of 4.3 by the RV_e of 6 results in a CS of 25.8, which corresponds to an RQ of 1000.

As seen from Table 9-2, the highest CS and lowest RQ are obtained from the inhalation study in mice by Yoshimura et al. (1979); therefore, the RQ for benzotrachloride is 10 (Table 9-3).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

The carcinogenicity of benzotrachloride was discussed in Section 5.1. and relevant studies are summarized in Tables 5-1 to 5-4. Oral administration of benzotrachloride to female mice at 0, 0.043, 0.17, 0.7 or 2.7 mg/mouse, 2 days/week (0, 0.4, 1.6, 6.7, 25.7 mg/kg/day, using 0.03 kg as the mouse weight) for 25 weeks followed by 78 weeks observation resulted in dose-related, significantly increased incidences of squamous cell carcinoma of the forestomach at ≥ 6.7 mg/kg/day and of lung adenoma/adenocarcinoma at ≥ 1.6 mg/kg/day and a significantly increased incidence of thymoma at 25.7 mg/kg/day (Fukuda et al., 1978) (see Table 5-1). Inhalation exposure of female mice to 1.6 ppm (12.8 mg/m³) for 30 minutes, 2 days/week for 12 months followed by an observation period of 12-15 months, resulted in a high incidence of lung tumors (Yoshimura et al., 1979). Similar results were obtained in female mice exposed by inhalation to 6.8 ppm (54 mg/m³) for 30 minutes, twice weekly for 5 months, followed by 5 months of observation (Takemoto et al., 1978). No controls were used in these studies. Fukuda et

TABLE 9-3

Benzotrachloride

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose*:	0.53 mg/day
Effect:	Increased mortality
Reference:	Yoshimuro et al., 1979
RV _d :	5.9
RV _e :	10
Composite Score:	59
RQ:	10

*Equivalent human dose

al. (1981) found increased incidences of skin carcinoma, lung adenoma/carcinoma and lymphoma of the thymus in female mice treated dermally with benzotrichloride in benzene compared with benzene-treated controls (see Table 5-2). In humans, data regarding the carcinogenic effect of benzotrichloride exposure alone were not available. Increased incidences of digestive and respiratory cancers were found among workers exposed to benzotrichloride, benzal chloride, benzyl chloride and toluene in the manufacture of benzoyl chloride and other chlorinated toluenes (Sakabe et al., 1976; Sakabe and Fukuda, 1977; Sorahan et al., 1983) (see Tables 5-3 and 5-4).

Results of mutagenicity tests of benzotrichloride in bacterial systems are equivocal. Yasuo et al. (1978) obtained positive results in a rec assay in Bacillus subtilis, in reverse mutation assays in Escherichia coli and Salmonella typhimurium in the presence of metabolic activation. Jagannath (1978), however, found negative results for reverse mutation in S. typhimurium and for forward mutation in Saccharomyces cerevisiae in the presence and absence of metabolic activation.

Based on the carcinogenicity studies in mice, IARC (1982b) concluded that there was sufficient evidence that benzotrichloride is carcinogenic in mice. IARC (1982b) also concluded that the epidemiological data of Sakabe et al. (1976) and the case reports of Sakabe and Fukuda (1977) were inadequate to evaluate the carcinogenicity of benzotrichloride alone, but that the data do provide limited evidence that a carcinogenic risk to humans is represented by employment in benzoyl chloride production. The study by Sorahan et al. (1983) was not available for review by the IARC (1982b) working group; however, this study strengthens the evidence that employment in the production of benzoyl chloride represents a carcinogenic risk to humans. Therefore, it is appropriate to classify benzotrichloride as an IARC group 2B chemical and CAG group B₂ (U.S. EPA, 1984).

The data used to calculate the $1/ED_{10}$ are presented in Table 9-4. The dose-response data for adenocarcinomas in the lungs of female mice treated by gavage (Fukuda et al., 1978) were used because these data generated the highest q_1^* (see Chapter 8) as well as the highest $1/ED_{10}$. The transformed doses were calculated by dividing the experimental doses by the reference mouse body weight (0.03 kg) and by multiplying by 2 days/7 days. This calculation results in the doses that appear in Table 5-1. To obtain the doses that appear in Table 9-4, a further correction is made by multiplying by le/Le . The unadjusted $1/ED_{10}$ was calculated using the multi-stage model developed by Howe and Crump (1982). The adjusted $1/ED_{10}$ (F) was calculated by multiplying the unadjusted value by the cube root of the ratio of the reference human body weight (70 kg) to the reference mouse body weight (0.03 kg) and by $(L/Le)^3$.

In a previous determination of the F-factor for benzotrichloride (Becker, 1984), the data for forestomach tumors in the study by Fukuda et al. (1978) were used as the basis; however, a higher value is obtained using the data for lung carcinomas.

Since the F-factor of $88 \text{ (mg/kg/dzy)}^{-1}$ falls between 10 and 100, benzotrichloride is placed in Potency Group 2. A chemical in Potency Group 2 with a CAG classification of B_2 has a MEDIUM hazard ranking according to the scheme for Reportable Quantities under CERCLA.

TABLE 9-4

Derivation of Potency Factor (F) for Benzotrichloride

Reference:	Fukuda et al., 1978
Exposure route:	oral (gavage)
Species:	mice
Strain:	ICR
Sex:	female
Vehicle or physical state:	sesame oil
Body weight:	0.03 kg
Duration of treatment:	25 weeks
Duration of study:	78 weeks
Lifespan of animal ^a :	104 weeks
Target organ:	lungs
Tumor type:	adenocarcinomas
Experimental doses/ exposure:	0.0, 0.043, 0.17, 0.7, 2.7 mg/mouse, twice weekly
Transformed dose (mg/kg/day):	0.0, 0.13, 0.52, 2.12, 8.24
Tumor incidence:	0/35, 1/37, 9/38, 16/40, 10/35
Unadjusted 1/ED ₁₀ :	2.798197 (mg/kg/day) ⁻¹
Adjusted 1/ED ₁₀ (F factor):	87.9738 (mg/kg/day) ⁻¹

NOTE: The goodness of fit using all five doses was not adequate; therefore, the high dose was dropped from the derivation of 1/ED₁₀

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APPENDIX
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN Internation
TOXLINE
TOXBACK 76
TOXBACK 65
RIECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
FEDERAL REGISTER

These searches were conducted in October, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation through 1984). Cincinnati, OH. 486 p.

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Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. IARC, WHO, Lyons, France.

ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1985. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

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USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. USDI Fish and Wildlife Serv. Res. Publ. 137. Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California. State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effect of Pesticides on Non-Target Species. PB-269605. Prepared for the U.S. EPA, Washington, DC.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. EPA 540/9-79-003. NTIS PB 80-196876. Office of Pesticide Programs, U.S. EPA, Washington, DC.